UNIVERSITY OF GONDAR

COLLEGE OF MEDICINE AND HEALTH SCIENCES

INSTITUTE OF PUBLIC HEALTH

INCIDENCE OF LOST TO FOLLOW UP AND ITS PREDICTORS AMONG HUMAN IMMUNODEFICIENCY VIRUS POSITIVE ADULTS AFTER INITIATION OF ANTIRETROVIRAL THERAPY AT PAWI GENERAL HOSPITAL, NORTHWEST ETHIOPIA, 2017

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Incidence of lost to follow-up and It's predictors among Human immunodeficiency virus positive adults after Initiation of Antiretroviral Therapy at Pawi General Hospital, northwest Ethiopia, 2017

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Examiner

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Acronyms/Abbreviation

AHR	Adjusted Hazard Ratio
ART	Antiretroviral Therapy
BMI	Body Mass Index
CD4	Cluster Of Differentiation 4
CI	Confidence Interval
CIF	Cumulative Incidence Function
CPT	Cotrimoxazole Prophylaxis Therapy
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
SHR	Sub Hazard Ratio
IPT	INH Preventive Therapy
IQR	Inter Quartile Range
LTFU	Loss To Follow Up
NVP	Never pine
OI	Opportunistic Infection
SNNP	South Nation And Nationality And People
TB	Tuberculosis
WHO	World Health Organization

Table of Contents

List of tables

List of Figures

Abstract

Introduction: Antiretroviral therapy has significantly reduced mortality and improved life expectancy of HIV-infected patients. However, the success critically depends on regular patient follow-up. Lost to follow-up have been emerged as legitimate threats to the long-term success of ART programs in resource-limited countries. However, no study has been done at all about incidence and predictors of lost to follow up among Human immunodeficiency virus positive adults particularly in the study area.

Objective: The study was aimed at assessing incidence of lost to follow-up and it's predictors among HIV-positive adults after initiation of antiretroviral therapy.

Methods: An institution based retrospective cohort study was carried out from January 01/2013 to December 30/2016 among all HIV-positive adults who initiate ART. The data were collected by using data extraction sheet. Cumulative incidence function was used to estimate the probability time of lost to follow-up. Moreover, bi-variable and multivariable sub-distribution regression model of competing risk regression were fitted for the potential covariates of lost to follow up. P-value ≤0.05 was significant predictors.

Results: Over all Cumulative incidence rate of the study was 11.6 (95% CI; 9.8 to 13.7) per 100 adult-years follow-up time. Total follow up time was 1175 adult-years. At the end of the follow-up, there were 22.6% LTFU, 4.2% death and 73.2% were alive and transfer out. Independently significant predictors of LTFU were being male (aSHR=1.47:95%: CI: 1.02-3.13), being in the age of 15-24 years (aSHR=3.22:95%: CI: 1.65-6.28), being on WHO clinical stage IV (aSHR=1.79:95%: CI: 1.02-3.13) and being received isoniazid preventive therapy (IPT) (aSHR=0.11:95%: CI: 0.06-0.18).

Conclusions: In this study the incidence of lost to follow-up was generally high in the first six months to one year after ART initiation. Continuous and comprehensive follow-up for at risk population is necessary to minimize LTFU.

Keywords: -lost to follow-up, cumulative incidence, competing risks regression, sub-distribution model, predictors, and associated factors, ART

1. Introduction

1.1. Statement of the problems

Unprecedented gains have been made in the expansion of services for ART in resource-constrained settings. According to WHO 2015 report from an estimated 17 million people were accessing life-saving ART with global coverage 46% (1). Based on a single point estimate, there were nearly 1.2 million people living with HIV/AIDS in Ethiopia with incidence rate of 1.2% and 1.3% in the country level and Benshangul gumuz region respectively **(**2) by end of 2013 in Ethiopia the number of patients ever started ART reached 439,301 (3)

ART has significantly reduced mortality and improved life expectancy of HIV-infected patients. However, the success critically depends on regular patient follow-up(4). LTFU negatively impacts on the immunological benefit of ART and increases AIDS-related morbidity, mortality, and hospitalizations(5, 6) and complicate program evaluation by biasing mortality estimates, and an important threat to the success of HIV treatment programs (7).

LTFU in ART is an obstacle to the success of ART programs in resource- limited countries and have been emerged as legitimate threats to the long-term success of these programs. LTFU was as high as 30–50 % in one year follow up in some programs (8) and 18.7% particularly in Ethiopia by the end of 2012 ART(3, 9). understanding the reasons that underlie patient attrition and establishing more reliable and comparable program evaluation worldwide(10, 11)

However, LTFU was still common and increasing in resource-limited setting countries including a study area, Benshangul Gumuz region, Ethiopia. In the region, there were the scarcity of data about lost to follow-up and there was no research done about incidence rate and risk factor of LTFU after ART initiation. As a result, this study will serve as a baseline data for program planers and policy makers working at various level of HIV care. Furthermore, it will serve as a baseline data for further researches.

1.2. Literature review

1.2.1. Incidence of Lost to Follow-Up

A systematic review study in Latin and Caribbean countries, the cumulative incidence of LTFU was 15.3 and 12.1 per person years for Honduras and Mexico, respectively (12). Another Study conducted in South Africa incidence rate of LTFU was estimated to be 10.9 per 100 person-years(13). The LTFU rate was 10 per 100 person-years ranged from 8.7 to 13.6 in Zambia (14).Besides incidence rate the proportion of LTFU was 15.5% in India (15), 17.7% in Sub-Saharan African (16), 15.6%, 27% and 36.6% in studies conducted in southeastern Nigeria(17), South Africa(18), and Cameron(19) respectively.

Studies conducted in Ethiopia showed that the incidence rate was 8.2 per 100 person years in Aksum-Northern Ethiopia(20). LTFU was 21.7%, 14.5%, 19.6% in Southern Ethiopia Hospitals(21), Hadiya-southern Ethiopia(22), Ethiopian public hospital clinic (23) respectively.

1.2.2. Factors associated with LTFU

1. Socio-demographic characteristics

There were identified significant factors associated with LTFU. These include sex, young age, occupations, being no formal education. Sex is a significant risk factor LTFU. A study was done in India, Cameron, Nigeria showed that male was higher risk factor of LTFU than female(15, 17, 19). Similarly, a study conducted in Northern Ethiopia showed that male have almost 3 times higher hazard rate of LTFU(CI: 1.31, 5.66)(24).

Age was significant risk factors of the LTFU in ART. A study conducted in Nigeria showed that young age was risk factor of LTFU (25). Another study done South Africa showed that the younger age significantly related to higher risk of LTFU(26). A similarly study did in Ethiopia at different regions in Hosanna, Mizan Aman, Oromia and Southern Ethiopia adolescents were at higher risk of LTFU(21, 27-29). In contradiction, a study conducted in Southeastern Nigeria showed that incidence LTFU Loss-to-follow-up is most common among patients aged 25–34 and 35–44 years and the lowest among those aged 15–24 years(17).

Educational status is significant risk factor LTFU. A study done in India showed that being having no education more likely risk of LTFU in ART(15). Similarly a study southern Ethiopia and showed that secondary or higher educational status protected against LTFU(21).

Occupation is also a significant risk factor for LTFU. A study done in Nigeria showed that being unemployed) was a significant risk factor to LTFU(25).similarly, a study conducted in Oromia, Ethiopia being having formal education were significant factors(28).

Marital status was also a significant socio-demographic variable studies conducted in Ethiopia survey and Oromia, Ethiopia (28, 30).

2.2. Clinical characteristics

CD4 count is significant risk factor for LTFU. A study done in India showed that the lower CD4 count was a high-risk factor for LTFU (15).A study conducted in sub-Saharan showed that patients higher baseline CD4 counts more risk factor for LTFU (16). A study conducted in southern Ethiopia showed that the risk of LTFU was higher in patients with baseline CD4 cell counts <200 cells/mm^3 (HR 1.7; 95% CIs 1.3-2.2) compared to baseline CD4 counts ≥200 cells/mm^3 Contradict(31), a study conducted in Ethiopia rural hospital showed that higher CD4 cell counts was increased hazard rate of loss to follow up(32).

WHO stage was a significant risk factor. A study conducted India showed that the risk of LTFU in patients with WHO clinical stage III (HR 0.6; 95% CIs 0.44-0.9) and clinical stage IV (HR 0.8; 95% CIs 0.6-1.0) lower compared to clinical stage I (15).similarly, in Ethiopia advanced WHO stage has a significant factors for (30)

Functional status was also a significant factor. A study conducted southern Ethiopia and Oromia showed that those whose bedridden functional status was increased the risk of LTFU(28, 31).

TB was a significant factor. A study conducted Aksum, Northern Ethiopia showed that those whose who are TB positive was increased the risk of LTFU. Additionally, TB prophylaxis INH was a significant independent variable in studies conducted in

Tigray, North-Ethiopia, Hosanna, Southern Ethiopia and Oromia, Ethiopia respectively(27, 28, 33).

ART regimen was a significant variable in studies conducted in Ethiopia (30). As far as ART regimen change was also independent significant variable in studies conducted in (Hosanna and Mizan-Aman)- southern Ethiopia-and Oromia-Ethiopia (27, 28, 33).

The other predictor variable that affects LTFU were adherence and nutritional status based on their body mass index. It was significant in studies conducted Oromia, Ethiopia, and Zambia respectively (27-29).

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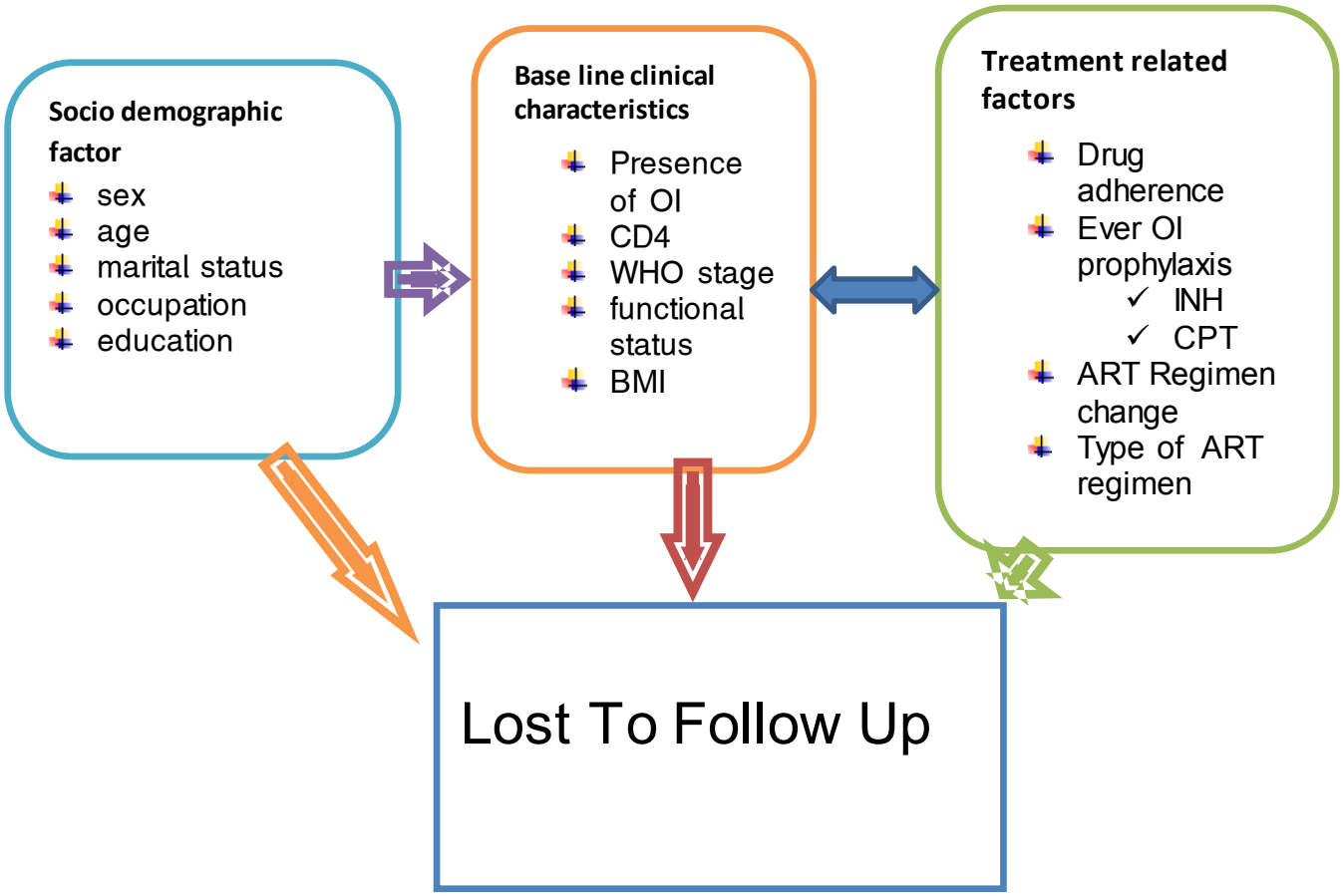

Figure 1 Conceptual Frame Work LTFU and its predictors among HIV positive adults on ART adapted from Literatures

1.3. Justification

There was a growing concern about the increasing rates of LTFU among HIV-positive adults starting ART; that leads to further disease progression, transmission, and cause for mortality and morbidity. It was still common and increasing in resource-limited setting countries including a study area, Benshangul Gumuz region, Ethiopia. In the region, there was scarcity of data about lost to follow-up and there was no research done about incidence rate and risk factors of LTFU after ART initiation. As a result, this study will be an input for decision makers working at various level of HIV care. Furthermore, it will serve as a baseline data and open the floor for further researchers.

2. Objectives

2.1. General objective:

To assess Incidence of LTFU and its Predictors among HIV-positive adults who were started ART from January 2012 December 30, 2016, in Paw General Hospital northwest Ethiopia, 2017.

2.2. Specific objectives:

To determine the incidence rate of LTFU among HIV-positive adults who initiate ART and;

To identify the predictors of LTFU among HIV-positive adults who initiate ART

3. Methods and Materials

3.1. Study area and period

The study was conducted in Pawi General Hospital from January, 01/2012 to December, 30/2016 which is found in Pawi woreda village 7, Metekel zone Benshangul Gumuz regional state, Ethiopia. Pawi is 410 Km away from the capital city of the region Assossa, and 570 Km away from Addis Ababa-Ethiopia. Apart from other services Pawi General Hospital give chronic HIV care and support for both pre-ART and ART service since 2005. They had 3210 patients ever enrolled into the care and 1760 had started ART in the hospital. Currently, there were 916 clients taking the service. There were 871 adults on ART service until December 30, 2016.

3.2. Study design

An institution based retrospective cohort study was carried out among HIV-positive adult patients.

3.3 Source population

All HIV-positive adults who registered on ART clinic in Pawi General Hospital, northwest Ethiopia

3.4. Study population

All HIV-positive adults started ART and whose charts existed at Pawi General Hospital ART clinic

3.5. Inclusion and exclusion criteria

3.5.1. Inclusion criteria

All HIV-positive adults who ever started ART at Pawi General Hospital ART clinic

3.5.2. Exclusion criteria

Those who had incomplete baseline data
Those whose outcomes were not defined

3.6. Sample size determination and sampling procedures

All HIV-positive adults who ever started ART in Pawi General Hospital ART clinic were included in the study. To check the sample size adequacy, sample size determination was calculated based on population proportion and predictor variable.

$$n = \frac{(z\alpha/2)^2 p(1-p)}{w^2}$$

Where w=margin of error measure of precision of estimate

P=is incidence rate of lost to follow up

$Z\,{}^{\alpha}/_{2}$ is the value of *Z* from standard normal curve at ${}^{\alpha}/_{2}$

Based on the study conducted in Aksum Northern Ethiopia by Haile K. in 2014 the incidence of lost to follow-up was 8.2 per 100PY(20)

$n = \frac{(1.96)^2 0.082\,(1-0.082)}{0.05^2}$**=115**

Based on predictor variables by using survival power formula with study conducted Mizan-Aman Hospital, southern Ethiopia, 2014(29).

Table 1: sample size determination for study conducted among HIV positive on ART adults at Pawi General Hospital from January 1, 2012 to December 30.2016.

Predictor variable	Assumption	Hazard ratio	Sample size
CD4	Power=80% CI=95%	δ =log(1.75)	**583**
Regimen change	Power=80% CI=95%	δ =log(5.51)	60
INH prophylaxis	Power=80% CI=95%	δ =log(3.72)	99

$$\mathrm{nev} = \frac{\left(\mathrm{Z1}-\frac{\alpha}{2}+\mathrm{Z1}-\beta\right)2}{\delta^2\,\Pi(1-\Pi)} \quad \text{and} \quad \mathrm{N} = \frac{\mathrm{nev}}{\mathrm{pev}}$$

Where Nev= is number of event (lost to follow up)

δ = log hazard ratio

Π=is the standardized effect difference of lost to follow up

pev= is the failure probability LTFU

Z1-α/2 and Z1-β= are the reliability coefficient of lost to follow up

N= the numbers of participants included in the study

Accordingly, the maximum sample size based on the above two formula was 115 and 583. Therefore the maximum sample was 583. The actual data collected in a study area were 602 which was higher than the expected

3.7. Study Variables

3.7.1. Dependent variable

Incidence of lost to follow-up, death as a competing event

3.7.2. Independent variables

Socio-demographic variables (age, sex, marital status, occupation, educational status)

Baseline clinical variables (Presence of OI, CD4, WHO clinical stage, BMI, and functional status)

Treatment-related variables ART adherence, Ever OI prophylaxis (INH and CPT), ART regimen change, Type of ART regimen)

3.8. Operational definitions

Lost to follow-up: Those Who were not taking an ART refill for a period of 3 months or longer from the last attendance for refill and not yet classified as 'dead' or 'transferred-out'

Time to Lost to follow-up: Was the time interval between the dates of ART initiation to LTFU.

Event: was lost to follow up from ART with in the study period.

Death: Those patients who died and confirmed by physicians.

Transferred out: Those patients who were formally transferred out to another health facility

Transfer in: Those patients who were formally transferred out from other health facility and entered to the hospital accordingly.

Censored: Those in any of the following events whichever comes first in five years follow-up time: If patients were transferred out to other health care center and if the patient were alive until the study period ends

3.9. Data collection methods and procedures

Data collection procedure: Data were collected based on structured data abstraction sheet/format from patients' cards and registers.

Data Source: The data for this research was secondary data recorded routinely in the hospital for clinical monitoring and evaluation purposes and entered into an electronic database and follow up medical records during the follow-up time ART.

Patient intake form, follow up card and ART registers, as well as the electronic information database, were used as data sources. Other clinical charts including laboratory test results were also used to collect the CD4 cell counts. Health Management Information System card number was used to identify individual patient cards or their data in the electronic database.

Socio-demographic characteristics, baseline and follow-up clinical and laboratory data, and the primary outcome variable (LTFU) from ART follow-up care after initiation of treatment, confirmed by reviewing medical registration at the hospital, noted by ART adherence supporters were collected from patient cards.

Data recording started from the date that patients started regular HIV care in the clinic until the end of the study to the confirmation of a final event in the study period were extracted by data abstraction sheet by trained nurses.

3.10 Data quality control

Training on the objective of the study and how to review documents as per data extraction sheet was given to data collectors and supervisions for one day before data collection was started. The data extraction sheet was pre-tested for consistency of understanding of tools and completeness of data for 11 charts. And necessary adjusted for the final data collection sheet was made. As well 3% random sample from data extracted was cross-checked its consistency, Whenever there appear incomplete, errors, and ambiguities of recording, the information formats were cross checked with the source card on the spot and

regular supervision was done. Besides there was data coding, rename, and clearing before analysis.

3.11. Data processing and analysis

Data exploration was carried out to check for any incompleteness, coding error and entered and cleared into EPI Info version 7. Then it was exported to Stata version 14.0 statistical packages for windows for further analysis.

Patients that were LTFU, died, who were transferred out and still in care at Pawi General Hospital ART clinic was identified and described. The main outcome variables were the incidence of LTFU and death. Patients' data is censored at the time of transferred out as well on the December 30/ 2016 are considered to be still in care at the time of censoring.

The patient cohort characteristics like age, CD4 count, time to LTFU and BMI described in terms of mean/median value and 25th & 75th percentiles and characteristics like sex, marital status, Occupational status, educational status, WHO clinical staging, OI, adherence, prophylaxis treatment, functional status, final outcome of study (alive, transferred out, death or LTFU) were described in terms percentages, frequencies (tables, graphs). Descriptive analyses of the continuous and categorical data describing the cohort's characteristics at baseline and during follow-up were also used for comparison. The outcomes of each patient were categorized into a status variable (0, 1, 2) as censored, lost and death respectively in competing risk model.

3.12. Statistical model and Analysis

3.12.1. Introduction

While censoring merely obstructs us from observing the event of interest, a competing event prevents the event of interest from occurring altogether. Because competing events are distinct from standard censorings, a competing risks analysis requires some new methodology and some caution when interpreting the results from the old methodology. Based on the method of Fine and Gray (1999), competing-risks regression provides a useful alternative to Cox regression (Cox 1972) for survival data in the presence of competing risks. This incorrect assumption of independent censoring can lead to an inflated estimation of the proportion of patients who were at risk of LTFU at time t, causing 1 minus

Kaplan-Meier to overestimate the LTFU probability which even notified the difference between the two estimates graphically.

The sub-distribution hazard for lost to follow-up is defined as the probability for a subject to fail from cause 'k' in an infinitesimal small time interval Δt, given the subject experienced no event until time t or experienced an event other than k before time t. They state that the estimated coefficient in the sub-distribution hazard model gives a consistent estimate of the so-called least false parameter $\hat{\beta}$ that can be interpreted as time-averaged sub-distribution hazard ratio.

3.12.2. Cumulative incidence

The 1 – KM curve overestimates the probability of LTFU at each follow-up time, since individuals who were dead were considered as censored. Death can be considered a non-random competing event whose occurrence obscures the occurrence of LTFU for that individual rather than prevent from seeing the event. Both the Kaplan-Meier survival curve (1 – KM) of lost to follow-up and the cumulative incidence function (CIF) in presence of competing risk were presented. The function CIF death(t) denotes the probability of experiencing the death event before time t and before the occurrence LTFU(34).

3.12.3. Sub-distribution hazards regression

Competing risk regression models was used to estimate crude and adjusted sub-hazard ratio (aSHR) and 95% CI for covariates of interest. Competing risk for LTFU was death. We adjusted for the effects of selected baseline and clinical characteristics in multivariable regression models. The variables in bi-variable data analysis with p-value below 0.25 was included the multivariable Sub-distribution hazards regression model to examine the effect of different covariates on lost to follow up. The Fine and Gray model for the sub-distribution hazard was used to model cumulative incidence. Patients with the competing event was kept at risk and continued to contribute person time, with the remaining time at risk(35).

It took into account the informative censoring nature of the competing risk events which can be described as a CIF regression model and had a direct link between sub-distribution hazards and Can now assess covariate effects on the CIF.(36). Which was used sub-distribution hazard regression to estimating actual risks and

prognosis and the overall impact of covariates on the incidence of the lost to follow up(37). The model was selected by Wald statics and Bayesian information criteria (AIC and BIC) (38-40) and the proportional assumption for the sub-distribution was checked by the schoenfeld residual test.

4. Ethical Consideration

Ethical clearance was obtained from the Institutional Review Board of the UOG institute of public health. Written informed consent was not feasible because this was secondary data retrieved from an electronic database and follow-up registration of the Hospital. Data were anonyms and handle confidentially during all phases of research activities. It had an open approval to use data from patients' records as long as patient confidentiality was not broken.

5. RESULT

5.1. Baseline socio-demographic characteristics of study participants

Out of 720 charts 602 were included in the final analysis. From those patients, 56.2% were females. The median age at ART initiation was 32 years with [IQR]: 27-39). About 44.5% of participants were ages between 25-34 years were whereas; nearly half of study participants were married. Many of 33.32% and 24.92% were farmers and daily labors respectively. Regarding to their educational status, 44.9% had no formal education whereas 36.9% had primary education (Table 2).

Table 2 Baseline socio-demographic characteristics among adult HIV-positive adults on ART at Pawi General Hospital, Northwest Ethiopia from Jan, 2012-Dec 30, 2016.

Variables		Frequency(n=602)	Percent (%)
Age			
	15-24 years	81	13.5
	25-34 years	268	44.5
	35-44 years	170	28.2
	>45 years	83	13.8
Gender			
	Female	338	56.2
	Male	264	43.8
Marital status			
	Never married	112	18.6
	Married	285	47.3
	Divorced	146	24.3
	Widowed	59	9.8
Educational status			
	No formal education	270	44.8
	Primary	222	36.9
	Secondary	95	15.8
	Territory(12+)	15	2.5
Occupation			
	Daily labor	150	24.9
	Farmer	200	33.2
	Merchant	67	11.1
	Government employee	48	8.0
	Self-employee	42	7.0
	Student	31	5.2
	House wife	64	10.6

5.2. Baseline clinical status of Adult HIV-positive on ART

Nearly half of patients were eligible for ART by WHO clinical stage and TLC while 48% of them were by CD4 cell count criteria. The mean baseline CD4 cell count was 217 (IQR: 119-341) cells. Regarding nutritional status, 42.4% of participants were malnourished. More than half 54% of the study participants have initiated ART at WHO stage III. Cotrimoxazole Preventive Therapy (CPT) and isoniazid Preventive Therapy (IPT) for TB were given for 69.4% and 56.2% respectively.

Nearly two third of the patients started ART treatment with TDF-3TC-EFV and 6% of the patients were substituted to another regimen within first line, and 2% switched to the second line. Over 97% of the participant's drug adherence was good (Table 3). Majority of study participants were working functional status. More than one-fifth of participants had OI of which 51.8% had TB followed by bacterial pneumonia 38.62% (Figure 2).

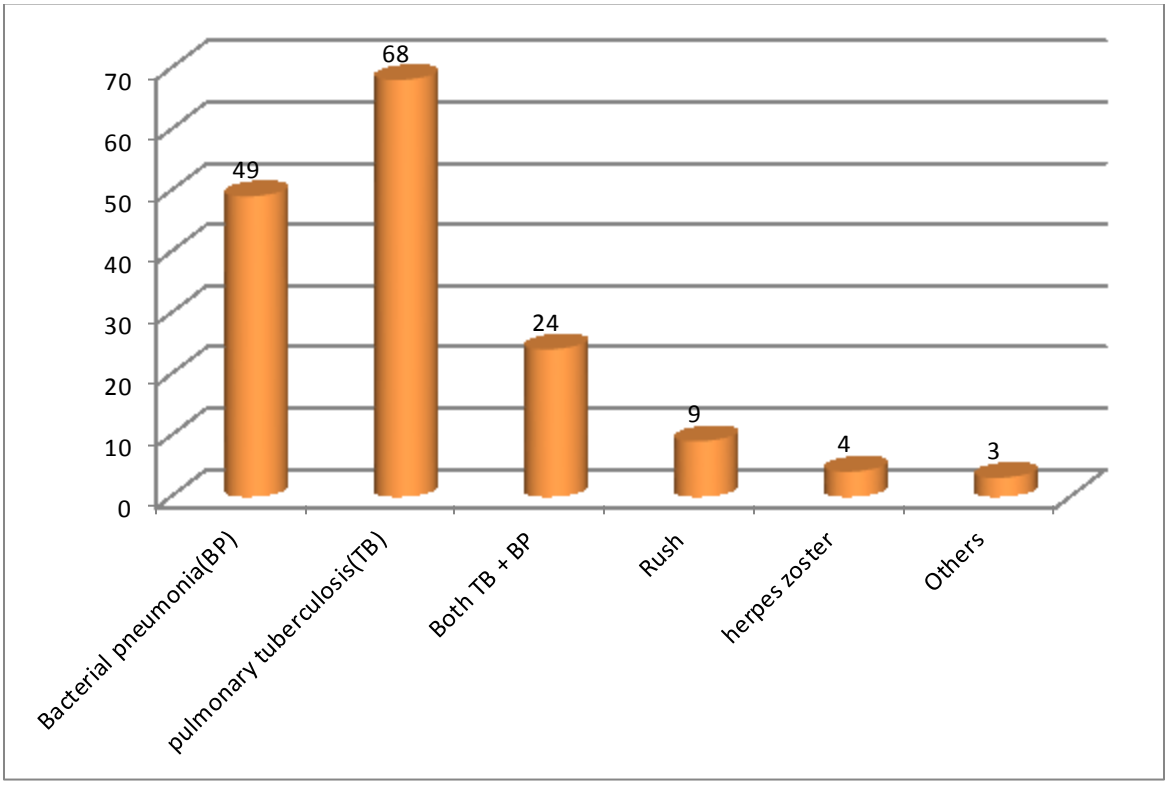

Figure 2 prevalence of opportunistic infection among HIV-positive adults on ART at Pawi General Hospital, northwest Ethiopia from January 1, 2012 to Dec, 2016

Table 3 Base line clinical characteristics of among HIV-positive adult on ART at Pawi General Hospital, northwest Ethiopia from Jan 1, 2012 to Dec, 30 2016

Variables			Frequency(N=602)	Percent (%)
IPT				
	Not received		262	43.8
	Received		340	56.2
CPT				
	Not receiving		184	30.6
	Receiving		418	69.4
Opportunistic infection				
	No OI		469	77.9
	Have OI		133	22.1
WHO Clinical stage				
	Stage I		55	9.1
	Stage II		172	28.6
	Stage III		325	54.0
	Stage IV		50	8.3
ART regimen				
	1c(AZT-3TC-NVP)		97	16.1
	1d(AZT-3TC-EFV)		26	4.3
	1e(TDF-3TC-EFV)		410	68.1
	1f(TDF-3TC-NVP)		69	11.5
Functional status				
	Working		444	73.8
	Ambulatory		99	16.4
	Bedridden		59	9.8
Adherence				
	Good		585	97.2
	Fair		12	2.0
	Poor		5	0.8
Regimen change				
	NO		555	92.2
	YES	First line	36	6.0
		Second line	11	1.8
Nutritional status (BMI)				
	Normal		347	57.6
	Malnourished		255	42.4
CD4 cell count(cell/mm3)				
	<=100 cell/m3		119	19.8
	101-200 cell/m3		141	23.4
	201-350 cell/m3		194	32.2
	>350 cell/m3		148	24.6

AZT-Zidovudine, **3TC-**Lamivudine**, NVP-**Nevirapine,

EFV-Efavirenz, **TDF-**Tenofovier

5.3. Incidence of lost to follow-up of HIV-positive adults

Among 602 HIV-positive adults on ART, a total follow-up time was 1175 adult-years observation with an incidence rate of 11.6 (95% CI 9.8 to 13.7) per 100 adult-years LTFU. The study subject followed for a minimum of three months and maximum of 60 months after initiated ART with median follow-up time of LTFU was 18 months. The median survival time of male is shorter than female which was 15 and 23 months respectively. Nearly half of the study subjects were lost to follow -up within the first six months and 72.8% were lost before a year. Death was 25(4.2%) and the remaining 73.3% were censored. The cumulative probabilities of lost to follow-up at 6, 12 and 24 months were 0.09, 0.17, 0.25 respectively and 0.29 within the time interval 36-60 months.

LTFU was used as the event of interest and death was considered as competing risk. So to illustrate the differences in cumulative probability of LTFU estimates given by two estimators (1 minus Kaplan-Meier and cumulative incidence), in the presence of death as a competing risk were compared (Figure 3).

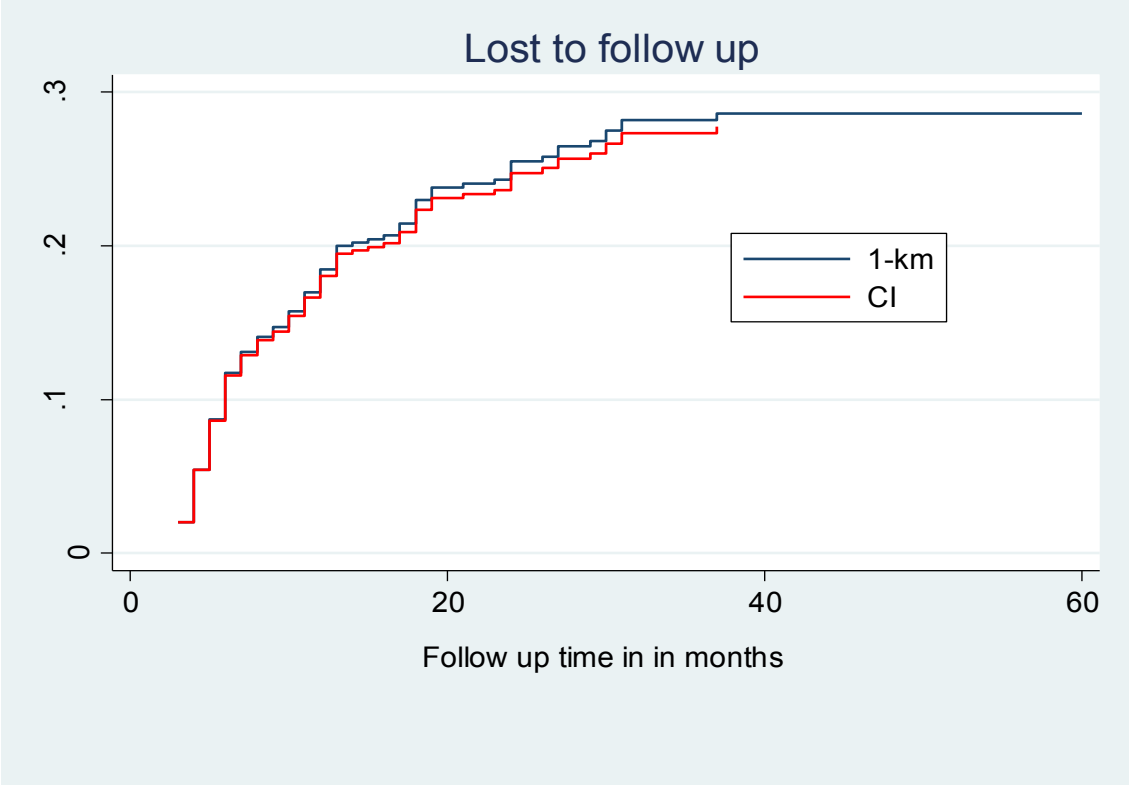

Figure 3 Kaplan-Meier and the CI curves among HIV-positive adults on ART at Pawi General Hospital, northwest Ethiopia from Jan, 2012 to Dec 2016.

5.4. Predictors of LTFU among HIV-positive adults

Test for equality of the incidence curves for categorical predictor variables was performed by using cumulative incidence. These of exploratory variables include age category, sex, WHO clinical stage and isoniazid prophylaxis, were significantly associated with LTFU of HIV-positive adults.

Based on the findings from the bivariate fine and gray/sub-distribution/ model analysis; age category, sex male, cotrimoxazole preventive therapy, WHO clinical stage, isoniazid Preventive Therapy, CD4 cell count, body mass index, drug regimen, opportunistic infection and functional status were predictors of LTFU. All ten covariates were fitted to the multivariable fine and gray model. Consequently, in multivariable sub-distribution sex, age category 15-24 years, not on IPT and, WHO clinical stage was significantly associated with LTFU of HIV-positive adults.

Age: Incidence rate of LTFU among age category 15-24 years, 25-34 years, 35-44 years and above 45 years were 256,101,122 and 61 per 1000 person- years respectively (Figure 4).

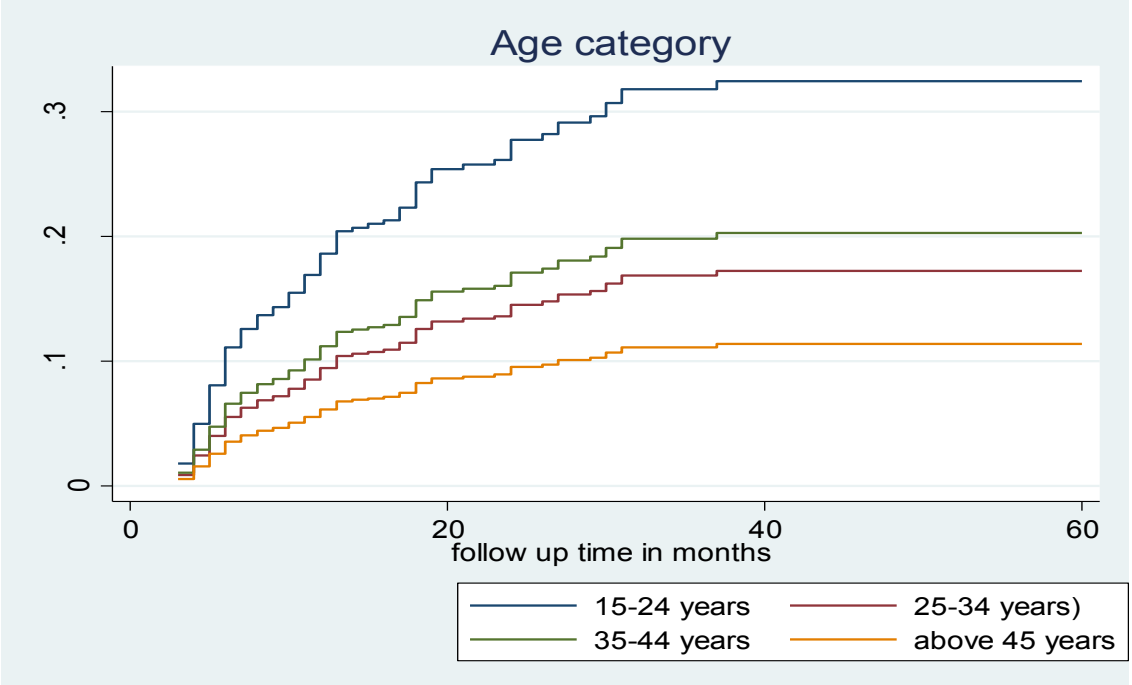

Figure 4: Cumulative incidence curve by age category among HIV-positive adult on ART at Pawi General Hospital, northwest Ethiopia from January 1, 2012 to December 30, 2016

Sex: Incidence rate of lost to follow up based on their sex were 90 and 123 per 1000 person years respectively.

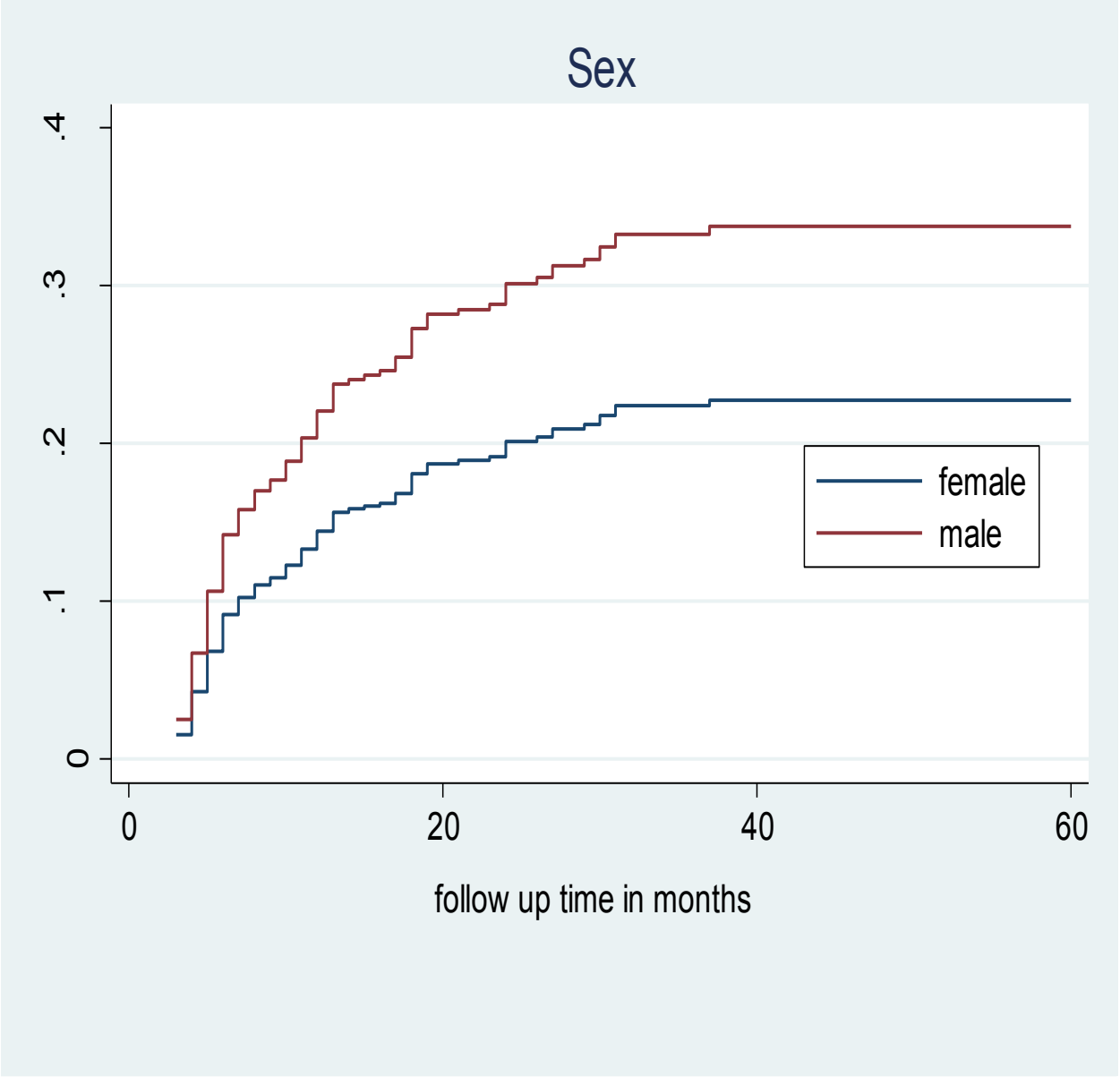

Figure 5: Cumulative incidence curve by sex among HIV-positive adult on ART at Pawi General Hospital, northwest Ethiopia from January 1, 2012 to December 30, 2016

WHO clinical stage: Incidence rate of lost to follow up among WHO clinical stage I/II, III and IV were 80, 123 and 249 per 1000 person years respectively.

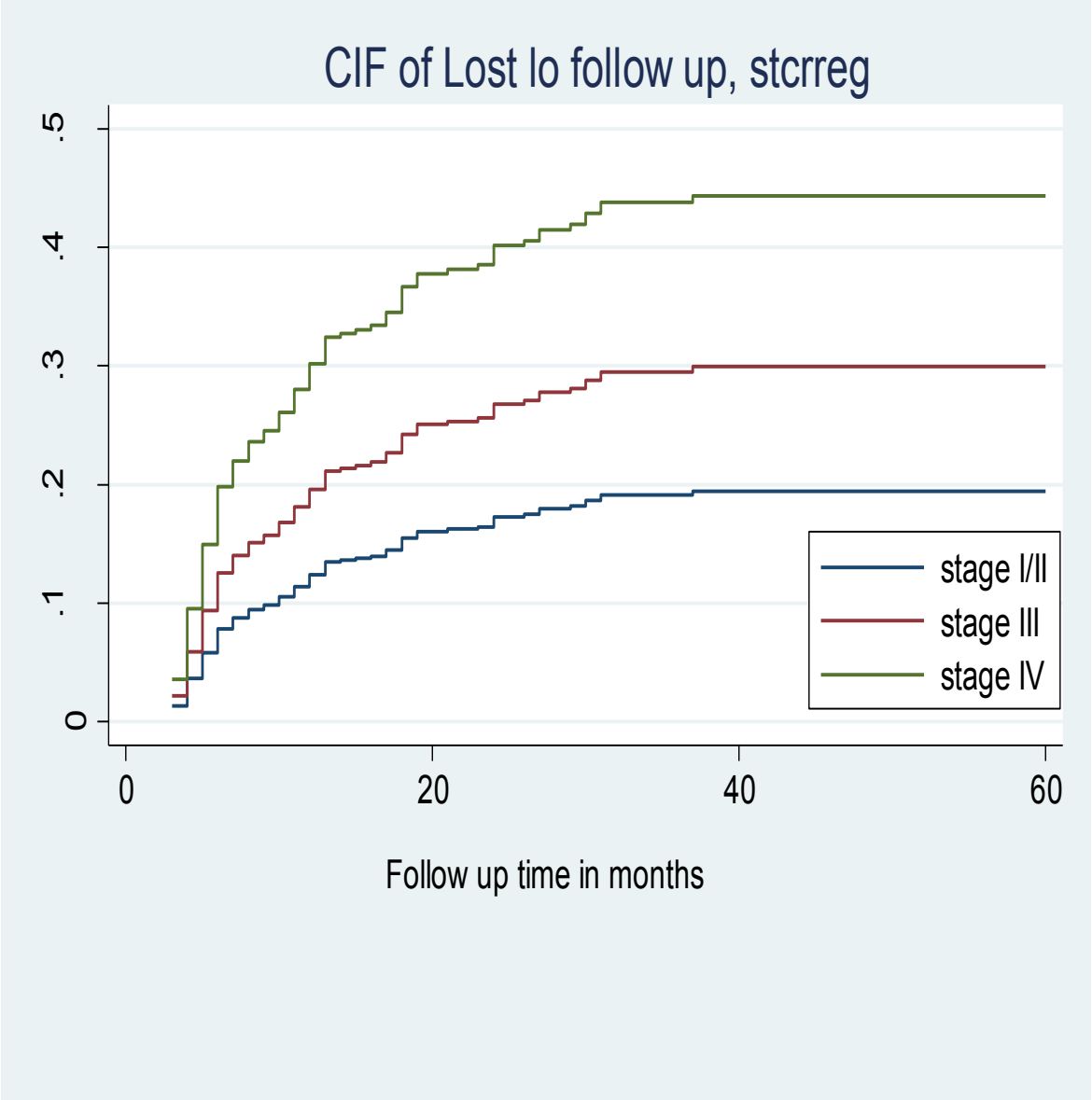

Figure 6: Cumulative incidence curve by WHO clinical stages among HIV-positive adult on ART at Pawi General Hospital, northwest Ethiopia from January 1, 2012 to December 30, 2016

Isoniazid Preventive Therapy prophylaxis :The incidence rate of LTFU up among clients who have received IPT were 309 per 1000 person years while not received INH was 26 per 1000 person years respectively.

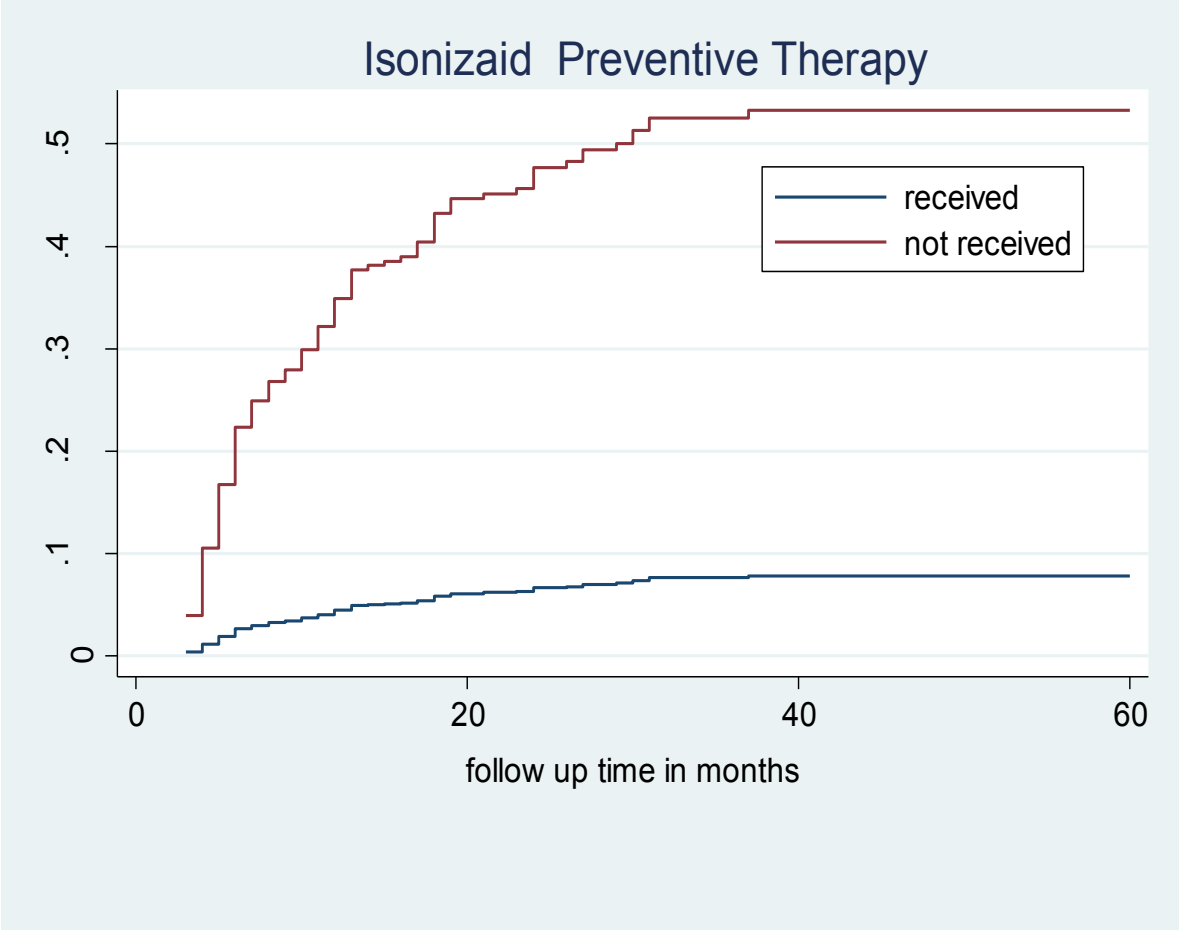

Figure 7: Cumulative incidence curve by isoniazid Preventive Therapy among HIV positive adults on ART at Pawi General Hospital, northwest Ethiopia from Jan, 2012 to Dec 30, 2016

Accordingly, being male adults increased the sub-hazard ratio of LTFU by 47% as compared to female adults (aSHR=1.47:95%: CI: 1.02-3.13). Adults whose age category between 15 and years increased the sub-hazard ratio of LTFU by 3.22 times as compared to those whose age category were above 45 years(aSHR=3.22:95%: CI:1.65-6.28). Those adults who were on WHO clinical stage IV increased the sub-hazard ratio of LTFU by 79% as compared to those adults with stage I and II (aSHR=1.79:95%: CI:1.02-3.13). Being on IPT lowered sub-distribution ratio for LTFU by 89% as compared to its counter parts (aSHR=0.11:95%: CI: 0.06-0.18). (Table 4)

Table 4: Multivariable competing risk regression analysis for predictors of LTFU among HIV-positive Adults at Pawi General Hospital, northwest Ethiopia, and January 1, 2012 to December 30, 2016

Variable	Survival status					
Time	**Lost**	**Death**	**Censored**	**cSHR:[95%CI]**	**aSHR:[95% CI]**	**P-value**
Age						
15-24 years	30	2	49	3.32[1.70-6.48]	3.22[1.65-6.28]	0.001*
25-34 years	53	13	202	1.46[0.78-2.72]	1.57[0.85-2.91]	0.152
35-45 years	41	5	124	1.82[0.90-3.46]	1.87[0.98-3.57]	0.058
>45 years	12	5	66	1	1	
Sex						
Female	63	12	262	1	1	
Male	73	13	179	1.60[1.14-2.23]	1.47[1.02-2.1]	0.038*
Nutritional status						
Normal	69	10	268	1	1	
Malnourished	67	15	173	1.38[0.99-1.93]	1.38[0.95-2.01]	0.095
WHO clinical stage						
Stage (I/II)	36	5	186	1	1	
Stage III	79	13	232	1.55[1.05-2.29]	1.24[0.83-1.83]	0.292
Stage IV	21	7	23	2.77[1.62-4.76]	1.79[1.02-3.13]	0.042*
Functional status						
Working	85	6	353	1	1	
Ambulatory	33	12	54	1.74[1.17-2.60]	1.03[0.66-1.60]	0.900

Table 4 (Continued)

Bedridden	18	7	34	1.46[0.89-2.37]	1.13[0.67-1.90]	0.649
Isoniazid						
Not received	115	22	125	1	1	
Received	21	3	316	0.11[0.07-0.17]	0.11[0.07-0.18]	<0.001*
CPT						
Not received	46	12	126	1	1	
Received	90	13	315	0.79[0.56-1.12]	0.98[0.66-1.47]	0.938
CD4 cell count						
<=100 cell/m3	30	17	72	0.91[0.56-1.46]	0.71[0.40-1.25]	0.232
101-200 cell/m3	30	4	107	0.73[0.46-1.17]	0.83[0.50-1.39]	0.479
201-350 cell/m3	38	1	155	0.67[0.43-1.05]	0.91[0.56-1.49]	0.712
>350 cell/m3	38	3	107	1	1	
Opportunistic infection						
No	93	13	363	1	1	
Yes	43	12	77	1.58[1.12-2.23]	0.87[0.61-1.26]	0.470
Regimen						
1c(AZT-3TC-NVP)	20	2	73	1	1	
1d(AZT-3TC-EFV)	3	0	23	0.58[0.18-1.89]	0.49[0.14-1.74]	0.272
1e(TDF-3TC-EFV)	97	17	295	1.37[0.85-2.21]	1.38[0.83-2.29]	0.216
1f(TDF-3TC-NVP)	16	6	48	1.09[0.58-2.05]	1.28[0.66-2.49]	0.465

*significant covariates, **cSHR**- crude Sub-Hazard Ratio, **aSHR**-adjusted Sub-Hazard Ratio

6. Discussion

This retrospective follow up study aim to assess the incidence of lost to follow up and its predictors among HIV positive adults after initiating ART. Several studies have shown that LTFU poses challenges to the successful implementation of ART programs in low and medium resource settings (8). LTFU can interrupt treatment, resulting in further disease progression, continued HIV transmission, negatively impacts on the immunological benefit of ART and increases AIDS-related morbidity, mortality, hospitalizations(5, 7, 8) and result in serious consequences, such as discontinuation of treatment, drug toxicity, treatment failure, and drug resistance(6)

In this study, the incidence rate was estimated to be 11.6 per 100 adult-years. Which was consistent with studies done in Lain and Caribbean countries with an incidence rate of (12.1-15.3)/100 person-year(12) and study done in South Africa(10.9/100 person-year)(13).On the other hand incidence rate in the current study was higher than studies in Zambia(8.7/100 person-year)(14) and Aksum, Northern-Ethiopia (8.2 per 100 person-years)(20). This variation might be explained by study settings difference, transfer to different health institution without prior information to their original health institution where they registered initially for proper recording and transfer out as can be supported with 19% transfer out rate findings, health seeking behavior and late initiation of the community as supported by the results delayed initiation of ART at advanced WHO clinical stage III and IV.

In addition to the incidence rate, proportion of LTFU for those studies not reported in person year observation was 22.6% which was lower than studies conducted in Cameroon 36.6%(19) and South Africa 27.6%(18), and consistent with studies conducted in southern nations nationality and people- Ethiopia 21.7%(21).on the other hand this finding also higher than studies done in India (15.5%), Sub-Saharan Africa (17.7%), Nigeria (15.6%), Hadiyia-southern Ethiopia 14.5% and Ethiopian public hospitals 19.6% (15-17, 22, 23) . This might be explained by travelling costs to the clinic since the study area were sparsely populated with limited-infrastructure directly or indirectly related to the study area were under developing region of Ethiopia with limited-resource and health service

As could be noted from the findings of multivariable findings in subdistribution hazard regression, in analyzing competing risks data: gender (male), age category (15-24 years), not on INH prophylaxis and WHO clinical stage IV were independent predictors of LTFU at 5% level of significance

Gender difference was detected independent predictors of LTFU, that male was increased the sub-hazard ratio of LTFU by 47% as compared to female. This finding was supported by studies conducted in India, Nigeria, Cameron and Aksum-Ethiopia (15, 17, 19, 24). This might be high mobility as far as most of the study participants male were daily labor and farmer, so they might haven't stable area they live.

Age category at 15-24(adolescence) was anther independent predictors of LTFU that Adolescents had 3.22 times higher sub-hazard risk of LTFU as compared to those who were above the age of 45 years. This finding was consistent with studies conducted in Southern Nigeria, South Africa, and southern Ethiopia (21, 25-28). This might be adolescent's particularly disobedient, showed immaturity in analytical thinking, and there may have been faced particular challenges associated with puberty. But this finding contradicted in a study conducted in Nigeria (17)that younger age groups were a lower risk of LTFU.

According, WHO clinical stage was independent predictors of LTFU. Those HIV-positive adults who were advanced clinical stage IV were 79% higher sub-hazard risk of LTFU as compared to those whose WHO clinical stage I/II. This evidence was supported by studies conducted in India and Oromia-Ethiopia (15, 30).They are also more likely to die due to ART side effects within the first 6 months of ART initiation. This was because another study indicated that half of LTFU in ART was due to death Nigeria (17).This study also showed that more than half of participant was in stage III and IV.

Moreover, Isoniazid Preventive Therapy prophylaxis was another predictors of LTFU; those who were received INH were lower the sub-hazard ratio of LTFU by 89% as compared to those who were not received IPT. This result was in line with studies conducted in southern Ethiopia, Northern Ethiopia and Oromia-Ethiopia (27, 28, 33). Isoniazid Preventive Therapy prophylaxis may have been impacted directly

or indirectly on LTFU which was recommended by national ART guideline to prevent the occurrence of TB-co-infection which was one of the causes of morbidity and mortality.

7. Limitation of the study

Since this is a retrospective cohort study, the data were already collected from patient's card which resulted incomplete information. As a result, unable to include important predictors like viral load and micronutrient deficiency (hemoglobin) and clinical factors (like side effects) were not well documented.

Strength of study considering death as a competing event improves the quality of estimation that avoided overestimation of one minus Kaplan-Meier by using cumulative incidence.

8. Conclusion

The higher LTFU incidence rate has been observed and more than half of LTFU was in the first six and twelve months.

Being male, age between 15-24 years, WHO clinical stage IV and not on INH prophylaxes were major independent baseline patient predictor's that affect incidence of LTFU.

9. Recommendation

For health care provider

- Close follow up of HIV positive adults on ART particularly during the first 6 month and one year is important to decrease lost to follow up
- Isoniazid preventive therapy prophylaxis increases the survival of patients, so better to encourage providing INH at the start of ART.
- Better to encourage Health education and promotion on early initiation before advanced WHO clinical stage
- Better to give especial emphasis on counseling, continuance follow-up and tracking for adults between age of 15 and 24 years.

For NGOs

- Strengthen monitoring and evolution at grass root level for the effectiveness of ART outcomes, especially on documentation system, provision of supplementary drugs for ART services like CPT and INH

For researchers

- Since LTFU incidence rate was high, better to find out true outcome of lost to follow-up
- The cumulative incidence will better be used in the presence of competing event that obscures the event of interest from happening
- Better to retrospective study was a full of inevitable incomplete information, so better to conduct prospective cohort study design to address behavioral factors

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ANNEX

Annex- Information Sheet

Title Of The Research Project: To assess lost to follow up and its predictors among adult people living with HIV who initiate ART in pawi General Hospital, northwest Ethiopia

Name of Principal Investigator: Moges Agazhe

Name of the Organization: Institute of Public Health, College of Medicine and Health Sciences, University of Gondar

Name of the Sponsor: self

Introduction: This information sheet was prepared For Pawi General Hospital administration and ART coordinating office .The aim of this information sheet was to make clear the above body about the research project, data collection procedure and to get permission to undertake the research.

Purpose of research: To assess lost to follow up and its predictors among adult people living with HIV who initiate ART in pawi General Hospital, northwest Ethiopia
Procedure: To achieve the above objective all HIV positive adults starting from January 2012 to December 2016 will be included in the study.

Risk and discomfort: By participating in this research there was no risk encountered to whom document is reviewed for data extraction.

Benefits: the research has no direct benefit for the patient whose record was reviewed but the indirect benefit for the participant and all others had a great impact for planning.

Confidentiality: The information collected from this research project was kept confidential and information about data that were collected by this study was stored without names, In addition, it was not revealed to anyone except the principal investigator and was kept locked with key and the data were collected by trained nurses who work in the ART clinic.

Incentives: There was no any incentive/ payment provided to take part in this project.

Persons to contact: If you have any question about the research project you can contact the advisors and principal investigators via the following address.

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Permission: lastly you are kindly requested to permit and forward your permission to the concerned body in your institution to get the data clerk and other responsible body.

Annex 2- Data abstraction sheet/Check list

Data collection format

This checklist was prepared for the collection of socio-demographic, clinical, treatment and outcome related information that are important for the assessment of LTFU and predictors LTFU who initiate antiretroviral therapy in Pawi general Hospital. All this information was retrieved from the clients ART and pre-ART registration book and from individual patient card without mentioning the name of clients. This information was collected by health care providers (BSc nurses) possibly working in the ART clinic of the hospitals.

Contact Information

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Part I: base line data (All adult patients who initiated ART in the year 2012-2016)

S.No	Variables	Categories
101.	MRN number	
102.	Age	_____yrs.
103.	Gender	1 Female 2 Male
104.	Marital status	Never married Married 3.Divorced 4. Widowed
105.	Education	1. No formal education 2. primary 3 .Secondary 4 .Tertiary
106.	Occupation	1. sex worker 3. daily labor 5. Farmer. 7. self-employed 2. driver 4. merchant 6. Government 8. others(s)
107.	Opportunistic infection	1. No 3. PTP 5. Rush 7. PCP 9. .Other(s) ------- 2. BP 4. EPTB 6. Diarrhea 8. Ulcer
108.	Past TB status	1. Yes 2. No
109.	ART start date	_____/_____/_____dd/mm/yyyy

110.	Base Weight	_____kgm			
111.	Base CD4 counts	_____cell/µl			
112.	Base WHO clinical stage	1. Stage I	2. Stage II	3. Stage III	4. Stage IV
113.	Base Functional status	1. Working	2. Ambulatory		3. Bedridden
114.	Original regimen	1a 1b	1c 1d	1e 1f	1g 1h
115.	ART Eligibility criteria	Clinical stage		CD4 count	3. TLC 4. Transfer in

Part III: Follow-up variables

start date mm/dd/yyyy	Eligibility	MRNo-	Sex	Age	Functional Status	Weight	Height	BMI	WHO stage	CD4 count	Screen for TB(P/N)	INH	CTX	Original regimen Code	Regimen change(Y /N)	OIS	Adherence	**Out come**

Final outcome	1. Alive	2. Death	3. Lost to follow up	4. Transfer out

Collected by: Name _____ Signature _____Date _____

Supervised by: Name _____ Signature _____Date _____

Declaration

I the undersigned, senior MPH student declare that this thesis is my original work in partial fulfillment of the requirement for the degree of master of public health in Biostatistics.

Name Moges Agazhe

Signature ----------

Place of submission institute of public health, college of medicine and health science, university of Gondar.

Date of submission ----------

This thesis work has been submitted for examination with our approval

Advisor(s)

Name	signature
1. Mr. Tadesse Awoke	----------
2. Mr. Kindie Fentahun	----------